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Expand on the severity of rebound pulmonary hypertension with discontinuation of iNO vs. iEPO.

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Answered on July 16, 2026

Analyzed query, searched for evidence ×2

Both **iNO and inhaled epoprostenol (iEPO) can cause rebound pulmonary hypertension upon abrupt discontinuation**, but the phenomenon is **better characterized and more clinically prominent with iNO**, while the rebound risk with iEPO — particularly in the inhaled form used in the ICU — is **less well-defined and appears to be clinically less severe** in practice.

Rebound Pulmonary Hypertension with iNO

Rebound PH after iNO withdrawal is a well-established and potentially life-threatening complication. The AHA/ATS defines it as a **>20% increase in PAP with a PAP-to-systemic pressure ratio >0.6**, associated with decreased cardiac output, hypotension, or systemic desaturation. Circulation Key features include:

- **Incidence:** Occurs in approximately **one-third of patients** during iNO weaning. Circulation
- **Severity:** Can be **life-threatening**, with signs including severe hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. Even patients who showed no initial hemodynamic improvement from iNO can develop rebound PH upon abrupt withdrawal. Circulation + 1
- **Mechanism:** Exogenous NO downregulates endogenous nitric oxide synthase (eNOS) activity. Research in lamb models demonstrated that iNO exposure decreases NOS activity by ~36%, mediated through endothelin-1 (ET-1)/ETA receptor signaling, superoxide production, and peroxynitrite-mediated nitration and inactivation of eNOS. This creates a state of impaired endogenous vasodilatory capacity upon withdrawal. Circulation Res...

- **Mitigation:** Gradual weaning to **<1–5 ppm** before discontinuation is recommended. Sildenafil (oral or IV) has been shown in randomized trials to attenuate rebound PH and shorten time to extubation. Dipyridamole has also been used. Circulation + 2

Rebound Pulmonary Hypertension with Epoprostenol

The rebound phenomenon with epoprostenol is most robustly described with **intravenous (systemic) epoprostenol** in chronic PAH, where abrupt interruption can lead to **rebound PH with symptomatic deterioration and even death**. Cochrane + 1 This is a well-recognized risk with chronic IV infusion, where complications such as pump malfunction or catheter obstruction can cause inadvertent interruption. Circulation

For **inhaled epoprostenol (iEPO)** specifically:

- The literature does not describe rebound PH with iEPO to the same degree as with iNO. While Lahm et al. note that "similar to iNO, abrupt discontinuation [of epoprostenol] may lead to rebound PH and even death," this statement is made in the context of systemic epoprostenol, and the same review highlights that nebulized/inhaled prostacyclins "forgo systemic side effects" and represent an attractive alternative to iNO. JACC
- iEPO acts through the **cyclic AMP (cAMP) pathway**, which is distinct from the cGMP pathway used by iNO. Importantly, iEPO does not appear to downregulate endogenous prostacyclin synthase in the same manner that exogenous NO suppresses eNOS, which may explain the **lower propensity for rebound**. Cochrane + 1
- In comparative studies, iEPO and iNO demonstrate **similar efficacy** in reducing mPAP and PVR, but the rebound phenomenon has not been a prominent safety signal in iEPO trials or observational studies. Circulation + 2

Summary Comparison

Feature	iNO	iEPO (Inhaled)	References
Rebound PH incidence	~33% during weaning	Not well quantified; appears lower	Circulation
Severity	Life-threatening (hypoxemia, hypotension, bradycardia, death)	Less well-characterized; severe rebound primarily described with IV formulation	Circulation + 2
Mechanism	Downregulation of endogenous eNOS via ET-1/superoxide/peroxynitrite	No analogous downregulation of endogenous prostacyclin synthase described	Circulation Res... + 1

Feature	iNO	iEPO (Inhaled)	References
Weaning strategy	Gradual wean to <1–5 ppm; sildenafil to attenuate rebound	Gradual dose reduction; no specific rebound-prevention protocol established	Circulation + 1
FDA warning	Boxed-level warning for rebound PH	No specific FDA warning for inhaled formulation rebound	FDA

In clinical practice, the **lower rebound risk with iEPO** is one factor — alongside significantly lower cost — that has driven many ICUs to favor iEPO over iNO. Circulation + 1 However, both agents should still be weaned gradually rather than discontinued abruptly, particularly in hemodynamically labile patients. Pediatric Pulmo... + 1

Would you like to explore the evidence on specific weaning protocols for iNO or iEPO, including the role of transitional agents like sildenafil or milrinone?

References

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9. Evaluation and Management of Pulmonary Hypertension in Noncardiac Surgery: A Scientific Statement From the American Heart Association.

And is the half-life of these medications a relevant factor?

10. Comparison of Inhaled Nitric Oxide With Aerosolized Prostacyclin or Analogues for the

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11. A Comparison of Inhaled Nitric Oxide Versus Inhaled Epoprostenol for Acute Pulmonary Hypertension Following Cardiac Surgery.
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Answered on 7/9/16, 2026

Analyzed query, searched for evidence

Yes, **half-life is a clinically relevant factor, but it does not fully explain the difference in rebound severity between iNO and iEPO** — the distinction is driven more by their differing effects on endogenous vasodilatory pathways than by pharmacokinetic duration alone.

Half-Life Comparison

Both agents have ultrashort half-lives, which is precisely what makes them attractive as selective pulmonary vasodilators in the ICU:

- **iNO:** Half-life is measured in **seconds** — NO binds rapidly to hemoglobin in the pulmonary vasculature, forming methemoglobin and nitrate, effectively inactivating it almost immediately upon reaching the bloodstream. Lancet + 1
- **Epoprostenol (inhaled):** Half-life is **3–5 minutes** in vivo. This is longer than iNO but still ultrashort, which is why both agents are considered titratable and appealing in the perioperative and ICU settings where hemodynamic goals change rapidly. European Respi... + 3

Why Half-Life Alone Does Not Explain Rebound Severity

If half-life were the primary determinant, one might expect iEPO — with its slightly longer half-life — to have a smoother offset and less rebound, and iNO — with its near-instantaneous inactivation — to have more abrupt loss of effect. While this pharmacokinetic difference may

contribute modestly, the **dominant mechanism** behind iNO's more severe rebound is its effect on endogenous vasodilator production:

- **iNO suppresses endogenous eNOS activity.** Exogenous NO exposure increases plasma endothelin-1 (ET-1) levels by ~120%, which activates ETA receptors, stimulates superoxide production, and generates peroxynitrite that nitrates and inactivates eNOS — reducing endogenous NOS activity by ~36%. Upon withdrawal, the patient has both lost the exogenous vasodilator and has impaired endogenous vasodilatory capacity, creating a "double hit." Circulation Res... + 1
- **iEPO does not appear to suppress endogenous prostacyclin synthase.** There is no analogous downregulation mechanism described for inhaled prostacyclins. When iEPO is discontinued, endogenous prostacyclin production remains intact, so the vasculature retains some baseline vasodilatory tone. JACC + 1

Clinical Implications

The ultrashort half-lives of both agents mean that the vasodilatory effect dissipates rapidly after discontinuation in either case. However, the critical difference is what happens to the **endogenous vasodilatory reserve**:

- With iNO, the combination of instantaneous drug offset plus suppressed endogenous NO production creates a vulnerable window for rebound PH, which is why gradual weaning to <1–5 ppm and bridging with sildenafil (a PDE5 inhibitor that preserves cGMP signaling) are recommended. Circulation + 2
- With iEPO, the slightly longer half-life provides a marginally more gradual offset, and preserved endogenous prostacyclin production provides a physiologic "buffer." Gradual weaning is still prudent in hemodynamically labile patients, but the rebound risk is clinically less concerning. JACC + 1

Notably, the AHA scientific statement on PH in noncardiac surgery highlights that both agents display short half-lives making them appealing perioperatively, and that efficacy and safety profiles are comparable — but the cost advantage of iEPO, combined with its more favorable rebound profile, has driven many centers to prefer it. Circulation

In summary, while the ultrashort half-lives of both agents are relevant to their rapid offset of action, the **mechanistic suppression of endogenous eNOS by iNO** — rather than the pharmacokinetic half-life difference per se — is the primary driver of the more severe rebound PH seen with iNO discontinuation.

Would you like to explore the specific protocols for transitioning from iNO to oral sildenafil or other agents to mitigate rebound PH during weaning?

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Follow-Up Questions

- List common patient populations who benefit most from inhaled nitric oxide or inhaled epoprostenol therapy?
- Discuss notable side effects unique to inhaled epoprostenol compared to inhaled nitric oxide?
- Outline monitoring strategies during transition or discontinuation of inhaled pulmonary vasodilators?